

REMARKS***Status of the Claims***

Claims 1, 17-18 and 22 and 26 are canceled; claims 2-5, 6-16, 19-21 and 27-28 are pending; claims 2-4, 6-7, 13-16 and 19-21 are amended; and claims 29-48 are added.

Claim 2 has been amended to recite that the antibody:

- i. is directed against a tumor-cell receptor associated glycosylation antigen;
- ii. inhibits MAPK activation in tumor cells and thereby inhibits activated MAPK mediated cell division; and
- iii. does not inhibit the glycosylated receptor from binding to its ligand.

Support for part i. of the amendment to claim 2 is found, for instance, in the specification, at page 1, paragraph 4. Support for parts ii. and iii. of the amendment to claim 2 is found, for instance, in Example I, at pages 15-18 of the specification.

Claims 2-5, 6-7, 13-16 and 19-21 have been amended to improve grammar.

Claim 6 has also been amended so that it recites that the antibodies inhibit (as opposed to prevent) a mitogenic stimulation of the tumor cells. Support for this amendment is found, for instance, in the specification, at page 17, lines 26-30.

Claim 13 has been amended so that it no longer recites preferred dissociation constants. New claims 31 and 32 depend from claim 13, and recite the dissociation constants formerly recited in claim 13.

Claim 14 has been amended so that it no longer recites preferred minimum doses. New claims 46 and 47 depend from claim 14, and recite the minimum doses formerly recited in claim 14.

Claim 19 has been amended so that it no longer recites particular body fluid or tissues. New claim 44 depends from claim 19, and recites that the body fluids or tissues of claim 19 are selected from the group of body fluids and tissues formerly recited in claim 19.

New claims 29 and 30 depend from claim 2, and recite that the antibody is IGN311 and ABL464, respectively. Support for claims 29 and 30 is found, for instance, in Examples I and II of the specification. (Pages 15-20).

New claim 35 is directed to a method for inhibiting division of tumor cells comprising administering to a patient an amount of antibody IGN311, antibody ABL364 or a combination thereof by which the IGN311 and/or ABL364 antibodies inhibit MAPK activation in said tumor cells and thereby inhibit activated MAPK mediated cell division but do not inhibit erbB receptor binding ligand. Support for claim 35 is found, for instance, in Examples I and II on pages 15-18 of the specification and in original claim 2.

New claim 36 recites:

- a method for stimulating chemotherapeutic agent mediated lysis of dormant tumor cells, micrometastases or both in a patient. Support for which is found, for instance, in the specification, at page 2, lines 16-28 and in the sentence bridging pages 5-6.
- administering to the patient an antibody directed against an erbB receptor comprising a tumor associated glycosylation antigen. Support for which is found, for instance, in the specification at page 4, lines 11-12.
- administering to the patient in combination with the antibody a chemotherapeutic agent. Support for which is found, for instance, in the specification at page 4, lines 21-23.
- that the administered antibody self aggregates and that the antibody is administered above these concentrations. Support for which is found, for instance, in the specification at page 19, lines 26-27.
- that the administration of the antibody at or above self aggregation concentration levels provides a growth stimulus to the dormant tumor cells and/or micrometastases. Support for which is found, for instance, in the specification at page 2, lines 26-28 and example II, pages 20-28.

New claim 37 depends from claim 36, and recites that the antigen is Lewis x, Lewis b, Lewis-y, sialyl-Tn, Tn antigen, GloboH, KH1, TF antigen or an alpha-1,3-galactosyl epitope Y. Support for claim 37 is found, for instance, in original claim 10.

New claim 38 depends from claim 36, and recites that the chemotherapeutic agent is radiation. Support for claim 38 is found, for instance, in the specification, at page 2, line 24.

New claim 39 depends from claim 36, and recites that the antibody is an IgG3 antibody. Support for claim 39 is found, for instance, in the specification at page 19, lines 20-28.

New claim 40 depends from claim 36, and recites that the growth stimulus comprises a mitogenic stimulation of the tumor cell and/or micrometastases mediated by activated MAPK. Support for claim 40 is found, for instance, in the specification at page 19, lines 20-28.

New claim 41 depends from claim 37, and recites that the antigen is Lewis-y. Support for claim 41 is found, for instance, in original claim 10.

New claim 42 depends from claim 40 or 41, and recites that the antibody is ABL364. Support for claim 42 is found, for instance, in the specification at page 19, lines 20-28.

New claim 43 depends from claim 42, and recites that antibody ABL364 is administered in a concentration of greater than or equal to 1 μ M. Support for claim 42 is found, for instance, in the specification at page 19, lines 20-28.

New claim 48 is directed to a method of treating a patient to reduce or inhibit the growth of tumor cells in a cancer by inhibiting glycosylated tumor some receptors comprising administering to a patient preparation consisting essentially of antibody directed against a receptor comprising a tumor associated glycosylation antigen. Support for claim 48 is found, for instance, in original claim 2 and in Example I of the specification.

No new matter has been added.

1. Claim Rejections under 35 USC Section 112, Second Paragraph

On page 3 of the Office Action, the Examiner rejects claim 2 as indefinite because it is allegedly

unclear whether the antibody directed against a tumor-associated glycosylation is directed to a "glycosylated tumor cell receptor" or to any glycosylated tumor-associated protein. Applicants respectfully traverse.

Applicants submit that the antibody of claim 2 is clearly directed against a glycosylation that is associated with tumors. Further, Applicants submit that a person of skill in the art would, upon reading the instant specification, plainly recognize that such tumor-associated glycosylations are post-translational modifications of tumor-associated proteins. Applicants therefore respectfully request reconsideration and withdrawal of the indefiniteness rejection of claim 2.

Also on page 3 of the Office Action, the Examiner rejects claim 4 as indefinite because it is allegedly unclear to what "chemotherapy-resistance" refers. Applicants respectfully traverse.

Applicants submit that the chemotherapy-resistance of the claim 2 is clearly refers to cancer cells of the patient that are resistant to chemotherapeutic agents. Accordingly, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection imposed against claim 4.

Also on page 3 of the Office Action, the Examiner rejects claim 5 as allegedly indefinite. Applicants have canceled claim 5, thereby obviating rejection.

Also on page 3 of the Office Action, the Examiner rejects claim 6 as allegedly indefinite for lacking antecedent basis for the limitation, "the mitogenic stimulation." Applicants have amended claim 6 to recite, "a mitogenic stimulation;" thereby obviating the rejection.

On page 4 of the Office Action, the Examiner rejects claim 7 as allegedly indefinite for lacking antecedent basis for the limitation, "the lysis of tumor cells." Applicants have amended claim 7 to recite, "a lysis of tumor cells;" thereby obviating the rejection.

Also on page 4 of the Office Action, the Examiner rejects claims 13 and 14 as allegedly indefinite for reciting the terms "most preferred" and "preferably." Applicants have amended claims 13 and 14 that they do not recite preferred embodiments of their ranges; thereby

obviating rejection.

2. Claim Rejections under 35 USC Section 102

The Examiner has rejected claims 2, 4, 5, 7-11 and 14-16 as allegedly anticipated by Saleh et al. as evidenced by Basu et al. and Kumar et al. (Office Action, pages 4-6). Applicants respectfully traverse.

In rationalizing the anticipation rejection, the Examiner asserts that the claims are drawn to:

“...a method of treatment comprising administering to a cancer patient an antibody directed against the aberrant glycosylation of a tumor-associated antigen, Lewis Y, to inhibit or reduce the growth of tumor cells in the patient by **inhibiting EGF binding to its receptor.**” (Office Action, page 4). (Emphasis added).

Here, the Examiner severely mischaracterizes the presently claimed tumor treatment methods. In particular, **no claim recites that the antibodies of the instant invention inhibit or reduce the growth of tumor cells by inhibiting EGF binding to its receptor**, as alleged by the Examiner. In sharp contrast, **the specification expressly discloses that the antibodies of the invention do not inhibit EGF binding to its receptor** (see *e.g.* Example II, page 18, lines 11-27).

The Specification further discloses that the antibodies of the invention:

- (i) are directed against a tumor cell receptor associated glycosylation antigen. (See, *e.g.* page 1, paragraph 4); **and**
- (ii) inhibit tumor cell growth which is mediated by the activation of MAPK when administered at appropriate concentrations. (See *e.g.* Example I, pages 15-18), **or**
- (iii) stimulate dormant tumor cell and/or micrometastases growth by activating MAPK independently of EGF when appropriately engineered to self aggregate and when administered at appropriate concentrations.

(See *e.g.* example II, page 19, lines 20-28).

Applicants further point out that the above-discussed properties of the antibodies of the present invention are not only disclosed in the specification, but also recited in the claims.

Based on the Examiner's mischaracterization of the antibodies used in the instantly claimed tumor/cancer treatment methods, the Examiner asserts that the disclosure by Saleh et al. regarding administering the antibody BR96-doxorubicin conjugate to cancer patients inherently anticipates the instant claims. (Office Action, page 5).

Here, Applicants respectfully remind the Examiner that well-established decisional law provides that inherent anticipation is appropriate only when the reference discloses prior art that **must necessarily** include the unstated limitation. Transclean Corp. v. Bridgewood Servs., Inc., 290 F.3d 1364, 1373 (Fed. Cir. 2002). (Emphasis added). That a feature in a prior art reference "could" operate as claimed does not establish inherency; nor is it sufficient if a material claim element or limitation is "merely probably or possibly present" in the prior art. In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999) and Trintec Indus., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed. Cir. 2002).

With these standards in mind, Applicants point out that the BR96 antibody taught by Saleh et al. does not necessarily have the MAPK activation/inhibition properties of the instantly claimed antibodies, which are independent of ligand binding to erbB receptor comprising a tumor-associated glycosylation. This is because there exists a multitude of epitopes within Lewis Y which present a vast number of possible antibody-epitope docking complexes, each with unique sterics that, in total, make it possible for any given antibody directed against Lewis Y to have virtually any effect on the biological activity of a Lewis Y modified receptor (*i.e.* ranging, for instance, from dominant negative to no effect to dominant positive).

But Saleh et al. is silent in regard to the impact that BR96 has on intracellular signaling pathways and MAPK mediated cell division; and it is not sufficient under In re Robertson that the Saleh et al.-taught BR96 antibody could or even probably inhibits/promotes MAPK mediated cell division in tumor cells and/or micrometastases, as do the presently claimed antibodies.

What is required for Saleh et al. to inherently anticipate the instantly claimed antibodies under Transclean is that BR96 must necessarily inhibit/promote MAPK mediated cell division in tumor cells and/or metastases, as do the presently claimed antibodies. Given that BR96 and the instantly claimed antibodies are made independently, Applicants submit that, for the above-presented reasons, it is at least more likely than not that BR96 recognizes a different Lewis Y epitope and has different biological activities than do the antibodies of the instant invention. Accordingly, the Examiner has failed to make a *prima facie* showing of inherent anticipation; and Applicants respectfully request its reconsideration and withdrawal.

Applicants also take this opportunity to point out that, in contrast to the Examiner's assertions on page 5 of the Office Action, the teaching of Saleh et al. regarding the patients selected for the reported toxicity study having failed no more than two (2) prior chemotherapeutic regimens and their disease not having progressed while on doxorubicin based therapy cannot be the disclosure of the "chemotherapeutic resistance" and "minimal residual disease" recited in claims 4 and 5. In particular, Applicants submit that it is well known that chemotherapy resistance involves a progression of the disease in the face of chemotherapy treatment. In addition, page 2, paragraph 6 of the instant specification discloses that a patient with dormant tumor cells is in an apparently healed state, which is in striking contrast to the apparent health of the patients selected for the Saleh et al. BR96 toxicity study.

For at least the foregoing reasons, Applicants submit that the instant anticipation rejection is improper, and respectfully request its reconsideration and withdrawal.

3. Claim Rejections under 35 USC Section 103

The Examiner has rejected claims 2-16, 19-21, 27 and 28 as allegedly obvious over Saleh et al. in view of Queen et al. (Office Action, page 6-8). Applicants respectfully traverse.

As discussed above in the anticipation section, Saleh et al. fails to disclose antibodies having the biological activities of the instant invention. Because Queen et al. fails to rescue those deficiencies, even the combination of Saleh et al. and Queen et al. does not teach the instantly claimed tumor treatment methods, and the Examiner has not established *prima facie*

obviousness. The obviousness rejection is therefore improper, and Applicants respectfully request its reconsideration and withdrawal.

4. Conclusion

In view of the foregoing amendments and remarks, it is believed that claims are allowable.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of \$450.00 is attached hereto.

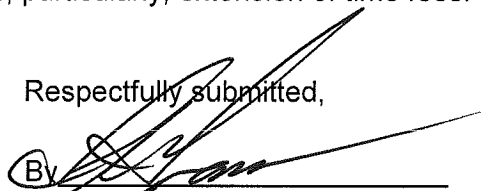
Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson, Registration No 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

- ☒ Attached is a Petition for Extension of Time.
- ☒ Attached hereto is the fee transmittal listing the required fees.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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